chemistry proceedings

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Proceedings

A New Synthesis of 3-Arylideneamino- and 3-Alkylideneamino-Substituted Hydantoins †

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† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Published: date

Abstract: A novel straightforward approach to 3-arylideneamino- and 3-alkylideneamino-hydantoins has been developed. It is based on reaction of readily available 4-(tosylmethyl)semicarbazones with NaCN in DMF followed by heating of the obtained α-(4-semicarbazono)nitriles with conc. HCl.

Keywords: 4-(tosylmethyl)semicarbazones; α-amidoalkylation; α-(4-semicarbazono)nitriles; 3-aminohydantoins

1. Introduction

Hydantoin, first described in 1861, and its derivatives are one of the most important representatives of imidazole family due to their easy availability [1–4] and a wide range of biological activities [5]. Among hydantoins, *N*-amino-substituted ones are especially interesting from a pharmaceutical point of view. For example, derivatives of 1-aminohydantoin such as dantrolene, azimilide, and nitrofurantoin are used as important drugs (Figure 1).

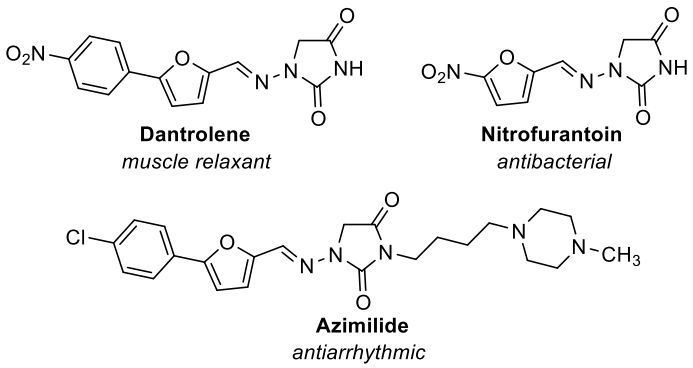
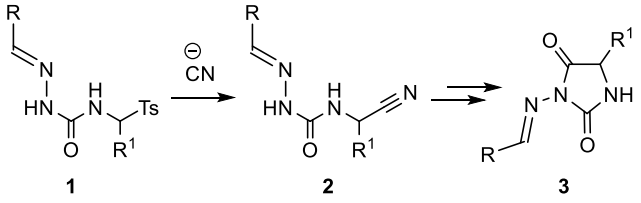


Figure 1. Examples of 1-aminohydantoin-based drugs.

It is also known that some 3-aminohydantoin derivatives are formyl peptide receptor modulators [6] and TNF-α inhibitors [7], show anticonvulsant [8], antihypertensive [9], antibacterial [10], and fungicidal activities [11]. However, in contrast to 1-aminohydantoins, their 3-amino analogues are much less studied. Described syntheses of 3-aminohydantoin derivatives from acyclic precursors generally involve formation of one or two C-N bonds (e.g., N3-C4 [8,12–15], C2-N3 [16–18], both N1-C2 and N3-C4 [19–23], both N1-C5 and N3-C4 bonds [24]). These compounds are also prepared using recyclizations of certain heterocyclic compounds [25–33]. It should be noted that there

are only a few reports on the synthesis of *N*-alkylidene- and *N*-arylidene-3-aminohydantoins. The latter, being analogs of 1-aminohydantoin pharmaceuticals (see Figure 1), can be considered as promising compounds in new drug discovery. They have been synthesized by condensation of 5,5-disubstituted 3-aminohydantoins with aldehydes [34,35], reaction of *N*-phenoxycarbonyl-hydrazones with *N*-substituted glycine esters [19,36], and treatment of hexahydro-1,2,4-triazine- 3,6-dione with 4-nitrobenzaldehyde or 4-dimethylaminobenzaldehyde in AcOH under reflux [33]. However, these methods suffer from various disadvantages, such as multistep procedures, poor synthetic flexibility, harsh reaction conditions, use of some toxic reagents, sometimes low yields, etc. Thus, the development of a new efficient approach to *N*-alkylidene- and *N*-arylidene-3-amino-hydantoins is of great importance.

Previously, we have described a general method for the synthesis of various 4-(tosylmethyl)semicarbazones **1** and demonstrated that they readily react with some *H*-, *O*-, *S*-, *N*-, *P*-, and *C*-nucleophiles to give the corresponding products of the tosyl group substitution [37]. We hypothesized that the use of cyanide anion as a nucleophile in this reaction could give access to nitriles of α-(4-semicarbazono)carboxylic acids **2**, which can serve as a starting material for the synthesis of *N*-alkylidene- and *N*-arylidene-3-aminohydantoins **3** (Scheme 1).



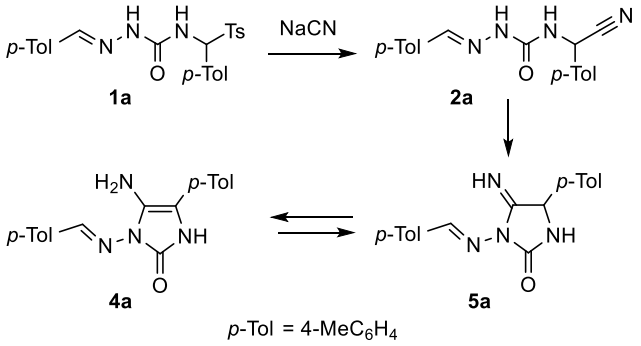
Scheme 1. Straightforward approach to *N*-alkylidene- and *N*-arylidene-3-aminohydantoins **3**.

Recently, we have shown that *N*-(tosylmethyl)-substituted ureas smoothly react with sodium cyanide in aprotic solvents to give the corresponding nitriles of α-ureidocarboxylic acids [38]. However, in the case of 4-(tosylmethyl)semicarbazones, the outcome of the cyanation is not obvious due to significant structural differences between ureido and semicarbazono groups.

Herein we report a novel straightforward approach to *N*-alkylidene- and *N*-arylidene-3-amino-hydantoins based on reaction of 4-(tosylmethyl)semicarbazones with sodium cyanide followed by acid catalyzed hydrolysis/cyclization of the resulting nitriles of α-(4-semicarbazono)carboxylic acids.

2. Results and Discussion

First, we studied the reaction of 4-(tosylmethyl)semicarbazone **1a** with NaCN under different conditions with varying reagents ratio, solvent, temperature, and reaction time. We found that, in general, this reaction resulted in the expected nitrile **2a** (Scheme 2).



Scheme 2. Reaction of sulfone **1a** with NaCN.

However, in contrast to the reaction of *N*-(tosylmethyl)ureas with NaCN [38], the outcome of the reaction of sulfone **1a** with NaCN is extremely sensitive to reaction conditions (Table 1). Using

DMF as a solvent, an increase in temperature (entry 1 vs. entry 2), reaction time (entry 3 vs. entry 4), and excess of NaCN (entry 2 vs. entry 3) lead to a significant increase in the number and amount of side products. Presumably, these side products arise from further transformations of the initially formed nitrile **2a** under the reaction conditions.

Table 1. Synthesis of nitrile **2a** by reaction of sulfone **1a** with NaCN under varios conditions.

Entry	Equiv. of NaCN	Solvent	Reaction Conditions	Yield of 2a (%) [a]
1	1.70	DMF	rt, 3 days	0 [b]
2	1.10	DMF	0 °C, 2.75 h	66 [c]
3	1.05	DMF	0 °C, 2 h	94 [d]
4	1.05	DMF	0 °C, 1 h	98
5	1.01	DMF	0 °C, 1 h	89 [e]
6	1.20 [f]	MeCN	rt, 24 h	0 [b]
7	1.10	MeOH	rt, 4 h	91 [g]
8	1.10	EtOH	rt, 4 h	87 [h]

[a] Isolated yield; [b] A complex mixture of numerous unidentified products along with enamine **4a**; [c] The product contains 15 mol% of enamine **4a**; [d] The product contains 3 mol% of enamine **4a**; [e] The product contains 4 mol% of sulfone **1a**; [f] In the presence of 18-crown-6 (0.2 equiv.); [g] The product contains 57 mol% of (*E*)-4-[(methoxy)(4-methylphenyl)methyl]-1-(4-methylbenzylidene)- semicarbazide [37] and 5 mol% enamine **4a**; [h] The product contains about 40% numerous by-products.

One of such transformations involves base-catalyzed cyclization of **2a** into imine **5a** or enamine **4a**. Indeed, the reaction of sulfone **1a** with NaCN (1.1 equiv.) in DMF (0 °C, 2.75 h) gave a mixture of nitrile **2a** along with a side product (Table 1, entry 2). ^{1}H NMR spectrum of the latter in DMSO-d_6 showed three singlet signals at 10.26, 9.81, and 5.01 ppm with relative intensities of 1:1:2, which can be assigned respectively to the NH, CH=N, and NH_2 protons in enamine **4a**. The structure of this compound was also confirmed by its ^{13}C NMR spectrum and DFT computational data (see below). Thus, this synthesis afforded a mixture of **2a** and **4a** in a ratio of 85:15.

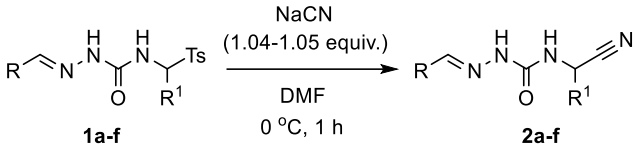
A significantly higher ability of nitrile **2a** to cyclize under basic conditions compared with nitriles of α-ureidocarboxylic acids [38] can be explained by increased NH acidity of semicarbazones. Deprotonation of the $N_{(2)}H$ in **2a** with NaCN gives the corresponding conjugated base followed by its cyclization into imine **5a** which tautomerizes into enamine **4a**.

We studied the behavior of nitrile **2a** towards various bases (NaCN, DBU, KOH, K_2CO_3, NEt_3) at room temperature. In all cases, a rapid conversion of **2a** into enamine **4a** and various other compounds was observed. For example, the treatment of **2a** with 0.05 equivalents of KOH in EtOH (rt, 2 h 23 min) followed by precipitation of the product with ice water afforded **4a** in 84% yield and about 70% purity (^{1}H NMR data). The ^{13}C NMR spectrum of **4a** in DMSO-d_6 showed the presence of signals at 149.8, 148.4, and 96.8 ppm corresponding to the CH=N, $C_{(2)}$, and $C_{(5)}$ carbon, respectively. These chemical shifts are consistent with those calculated for the most stable conformer of tautomeric structure **4a** (148.3, 152.8, and 88.9 ppm, respectively) by the GIAO method at the WC04/6-311+G(2d,p) level of theory using the DFT B3LYP/6-311++G(d,p) optimized geometries (DMSO solution, the PCM solvation model) and significantly differ from those calculated for the most stable stereoisomer of tautomeric structure **5a** (149.1, 158.1, and 53.6 ppm, respectively). The DFT calculation also demonstrated that the most stable stereoisomers of **5a** and **4a** are quite close in stability in DMSO solution (ΔE = 0.09 kcal/mol and ΔG = 0.72 kcal/mol in favor of **5a** with (*Z*)-configuration of the C=N double bond). Thus, it can be assumed that these stereoisomers are in dynamic equilibrium in DMSO. Apparently, some deviation of the calculated and experimental chemical shifts in the ^{13}C-NMR spectrum of compound **4a** (see above) can be explained by this equilibrium.

Under the optimized conditions, the reaction of **1a** with 1.05 equivalents of NaCN (DMF, 0 °C, 1 h) followed by precipitation of the product with ice water afforded cyanide **2a** in 98% yield and

excellent purity (Table 1, entry 4). The use of other solvents (MeCN, MeOH, EtOH) in the reaction of sulfone **1a** with NaCN resulted in quite unsatisfactory purity of **2a** (entries 6-8).

These optimal conditions were next applied to the reaction of sulfones **1b-f** with NaCN providing the expected nitriles **2b-f** in yields of 86–93% and high levels of purity (Scheme 3, Table 2).



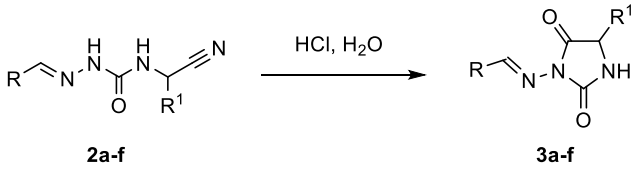
Scheme 3. Synthesis of nitriles of α-(4-semicarbazido)carboxylic acids **2a-f**.

Table 2. Reaction 4-(tosylmethyl)semicarbazones **1a-f** with NaCN under optimized conditions [a].

Entry	Sulfone	R	R^1	Product	Yield (%) [b]
1	**1a**	4-MeC_6H_4	4-MeC_6H_4	**2a**	98
2	**1b**	Ph	Ph	**2b**	86
3	**1c**	4-EtC_6H_4	4-EtC_6H_4	**2c**	95
4	**1d**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2d**	93
5	**1e**	4-MeC_6H_4	Pr	**2e**	93
6	**1f**	4-EtC_6H_4	Et	**2f**	89

[a] 1.04-1.05 equiv of NaCN, DMF, 0 °C, 1 h; [b] Isolated yield.

Next, we studied acid-catalyzed hydrolysis of nitriles of α-(4-semicarbazido)carboxylic acids **2a-f**. Previously, we demonstrated that treatment of α-ureidonitriles with conc. HCl at room temperature gives the corresponding amides in high yields [38]. In contrast, the reaction of nitrile **2a** with conc. HCl at room temperature for 24 h afforded hydantoin **3a** as the main compound (Scheme 4) together with various side products (about 40%, ^{1}H NMR data), among which enamine **4a** was observed (**3a**/**4a** = 87:13). Similar results were obtained when nitrile **2b** was reacted with conc. HCl at room temperature.



3 a R = R^1 = 4-MeC_6H_4; **b** R = R^1 = Ph; **c** R = R^1 = 4-EtC_6H_4;
d R = R^1 = 4-$MeOC_6H_4$; **e** R = 4-MeC_6H_4, R^1 = Pr;
f R = 4-EtC_6H_4, R^1 = Et.

Scheme 4. Acid-catalyzed hydrolysis of (4-semicarbazono)nitriles **2a-f** to give hydantoins **3a-f**.

Treatment of nitrile **2a** with conc. HCl at 39 °C for 7 h or 20 h did not improve the hydrolysis efficiency. Only when heating of **2a** in conc. HCl (boiling water bath, 40 min) was used, spectroscopically pure hydantoin **3a** was obtained in 82% yield. Under similar conditions, hydantoins **3b-e** were prepared from nitriles **2b-e** in 51–85% yields. In the case of nitrile **2f**, the hydrolysis was not so straightforward, and hydantoin **3f** was isolated only in a 14% yield.

3. Conclusions

In summary, a novel straightforward approach to *N*-alkylidene- and *N*-arylidene-3-aminohydantoins has been developed. This approach is based on reaction of readily available 4-(tosylmethyl)semicarbazones with sodium cyanide in DMF (0 °C, 1 h) followed by treatment of the obtained nitriles of α-(4-semicarbazono)carboxylic acids with conc. HCl (boiling water bath, 40 min).

Acknowledgments: This research was financially supported by the Russian Foundation for Basic Research (Grant No. 20-03-00928).

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